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Most Patients with Colorectal Tumors at Young Age Do Not Visit a Cancer Genetics Clinic

ORIGINAL CONTRIBUTION

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PURPOSE: This study examined the referral process for genetic counseling at a cancer genetics clinic in patients with colorectal cancer and to search for determinants of variation in this referral process.

METHODS: Patients who were recently diagnosed with colorectal cancer at a young age or multiple cancers associated with Lynch syndrome, hereditary nonpolyposis colorectal cancer, (N=119) were selected from PALGA, the nationwide network and registry of histopathology and cytopathology in the Netherlands. In a retrospective analysis, we examined whether these patients visited a cancer genetics clinic and identified determinants for referral to such a clinic. Factors of patients, professional practice, and hospital setting were explored with logistic regression modeling.

RESULTS: Thirty-six (30 percent) patients visited a cancer genetics clinic. Seventy percent of patients whom the surgeon referred to a cancer genetics clinic decided to visit such a clinic. Analysis of determinants showed that patients with whom the surgeon discussed referral and that were treated in a teaching hospital were more likely to visit a cancer genetics clinic.

CONCLUSION: The referral process is not optimally carried out. To deliver optimal care for patients suspected of hereditary colorectal cancer, this process must be improved with interventions focusing on patient referral by surgeons and raising awareness in nonteaching hospitals.

KEY WORDS: Colorectal neoplasms; Hereditary nonpolyposis; Genetic counseling; Quality of health care; Referral and consultation.

INTRODUCTION

Colorectal cancer (CRC) is the second leading cause of death from cancer in Western society. Up to 10 percent of adults have a first degree relative with CRC,¹ which increases their risk of developing CRC. The relative risk to develop CRC in families with multiple first-degree relatives is 4 to 6.²

The most common type of hereditary CRC is Lynch syndrome defined as a germline mutation in one of the DNA mismatch repair genes and formerly known as hereditary nonpolyposis colorectal cancer, which is an autosomal dominant disease. Lynch syndrome is characterized by early onset CRC and by multiple episodes of CRCs.³ In addition, extracolonic cancers occur including carcinomas of the endometrial, ovaries, small bowel, stomach, sebaceous gland, biliary tract, and upper urinary tract. Although Lynch syndrome accounts for about 1 to 3 percent of CRCs,⁴⁻⁷ it is crucial to identify Lynch syndrome because surveillance reduces morbidity and mortality by 65 percent over 15 years in unaffected relatives and reduces the risk of recurrence of CRC in patients.⁸ Optimal care for patients at high risk of Lynch syndrome or another hereditary CRC includes referral by clinicians to genetic counseling at a cancer genetics clinic.

The first and most important part of the referral process is the identification of patients suspected of hereditary CRC by the treating physician. After the identification of such patients, the next step is discussion of referral to genetic counseling at a cancer genetics clinic by the treating physician. The last part of the referral process is the patients' decisions to visit such a clinic.

The extent that the referral process occurs is unknown. The identification of patients with hereditary CRC is not optimal yet. For example, the Bethesda guidelines⁹ describe

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which patients merit microsatellite instability analysis and are widely used by genetic counselors; however, these guidelines are not well known by clinicians outside genetics departments.^{10,11} When identification of such patients is difficult, referral is possibly not discussed with all patients that are considered to benefit from genetic counseling. Regarding the decision of the patient to visit a cancer genetics clinic, one study demonstrates that 26 percent of patients, who are invited by letter, visit a cancer genetics clinic;¹² this percentage is unknown in recently diagnosed patients with whom referral is provided by their own treating physician.

Accordingly, data on the referral process to genetic counseling at a cancer genetics clinic is a first step to improve the care for patients suspected of hereditary CRC. Subgroups of hospitals, professionals, or patients in which the referral process is not optimally carried out may exist; hence, these subgroups need special attention to improve the referral process. Therefore, identification of determinants of the referral process at hospital, professional, and patient level is useful.

The aim of this study was to examine actual care regarding the referral process to genetic counseling at a cancer genetics clinic in the Netherlands.

METHODS AND MATERIALS

Study Population

An observational study was performed to assess actual care and determinants of variation in care for patients suspected of hereditary CRC. The study comprised 17 nonuniversity hospitals in the Netherlands. Patients were selected by PALGA, the nationwide network and registry of histopathology and cytopathology in the Netherlands. A search was performed to select consecutive patients, who complied with the four selection criteria. The first three selection criteria were chosen because they represent the revised Bethesda guidelines that are independent of family history or of the exact tumor type.¹³ The last criterion was added because these patients are at high risk of developing CRC at a young age. The selection criteria were: (1) CRC below the age of 50 years, or (2) second CRC below the age of 70 years, or (3) CRC and extracolonic cancer associated with Lynch syndrome below the age of 70 years, or (4) a colorectal adenoma with high-grade dysplasia below the age of 40 years. The patients were diagnosed between April and December 2004. The study was performed according to the rules of the Committee on Research Involving Human Subjects, Region Arnhem-Nijmegen.

Data Collection

Referral Process to a Cancer Genetics Clinic. The referral process consists of three parts: the identification of patients,

the referral by the treating physician, and the decision of the patient. We analyzed the referral process as a whole and as the patient decision. The referral process was considered optimally carried out when the patient actually visited a cancer genetics clinic for genetic counseling. In the Netherlands, cancer genetics clinics are associated with university medical centers. Some nonuniversity hospitals have outpatient clinics for genetic counseling. To examine the rate of patients that visited a cancer genetics clinic, these clinics were asked to check whether the patients selected by PALGA had visited.

Furthermore, we examined the patient decision to visit a cancer genetics clinic. A subgroup of patients with whom the surgeon discussed referral to genetic counseling as documented in the surgical record comprised this analysis group.

Determinants for the Referral Process. Determinants at the patient, professional, and hospital level that could explain the variation in the referral process were collected as follows:

- 1) Patient characteristics included age, sex, the criterion of inclusion, presence of cancer in the family, and survival. Survival was measured until the end of 2006. These data came along with the selection of patients by PALGA, except for presence of cancer in the family and survival. Family history was determined by surgical record search, and the survival status was checked in the hospital administration system. Presence of cancer in the family was defined as any cancer, because we considered taking a family history of any cancer as awareness of potential genetic cause of cancer.
- 2) Professional performance characteristics included description of family history and referral to a cancer genetics clinic obtained from surgical record search. When a family history was described, the source noted whether the surgeon described it or another clinician. For example, if a family history was obtained from a letter from an oncologist, a general internal specialist, or a general practitioner, this was captured.
- 3) Hospital characteristics included size, teaching status, and presence of an outpatient clinic for genetic counseling and were captured by interviewing surgeons and were obtained from hospital websites.

Two independent researchers performed the surgical record search. Double surgical record search was carried out in 9 out of 17 hospitals, and the agreement between these researchers was substantial for 'cancer in the family' and 'family history described' ($\kappa=0.75$ and 0.67 , respectively) and almost perfect for 'registration that referral to a cancer genetic clinic was discussed with patient' ($\kappa=0.81$). Data sheets were made anonymous after surgical record search, and data were entered into a database.

Statistical Analysis. Descriptive statistics described the referral process for genetic counseling at a cancer genetics clinic. Patient, professional, and hospital determinants were

analyzed for 'patients that visited a cancer genetics clinic' and 'patients that did not visit a cancer genetics clinic'. Correlation between determinants was checked. If a correlation coefficient greater than 0.4 was detected between two determinants, only one determinant was tested. Multilevel analysis showed that the rate of patients that visited a cancer genetics clinic did not vary significantly between hospitals (ICC=0). For this reason, a logistic regression model without correction for clustering was used to assess determinants for the referral process. The rate of patients that visited a cancer genetics clinic formed the dependent variable, and the possible determinants formed the independent variables. The percentage of variation that the independent variables could explain was calculated using Nagelkerke R^2 . Odds ratios (OR) were calculated to describe associations between the determinants and the rate of patients that visited a cancer genetics clinic. An OR greater than 1 meant a positive association. Two-sided P values of <0.05 were considered as statistically significant. Analyses were performed with the SAS system for Windows Version 8.2. (SAS Institute, Cary, North Carolina).

RESULTS

Referral Process to a Cancer Genetics Clinic

The study population selected by PALGA consisted of 119 patients: 62 males and 57 females. The mean age was 45.4 years (range: 26–69). Most patients ($n=99$) had CRC below the age of 50 years (Table 1).

Of 119 patients, 36 patients (30 percent) visited a cancer genetics clinic. Surgical records of 100 of 119 patients were available for review (33 records for patients that visited a cancer genetics clinic and 67 records for patients who did not visit respectively).

Family history was described somewhere in the surgical record of 88 percent of patients ($n=29$) that visited a cancer genetics clinic and 64 percent of patients ($n=43$) that did not visit a cancer genetics clinic. A family history of cancer was present somewhere in the surgical record of 61 percent of patients ($n=20$) who visited a cancer genetics clinic and of 34 percent of patients ($n=23$) who did not visit. The surgeon had described the family history in 51 percent of patients ($n=17$) who visited a cancer genetics clinic and in 28 percent of patients ($n=19$) that did not visit. The surgeon discussed referral to genetic counseling at a cancer genetics clinic with 48 percent of patients ($n=16$) that visited a cancer genetics clinic and with 10 percent of patients ($n=7$) that did not visit a cancer genetics clinic (Table 1).

Six of 17 hospitals had an outpatient clinic for genetic counseling. Forty-two percent of patients ($n=15$) who visited a cancer genetics clinic and 27 percent of patients ($n=22$) who did not visit were treated in a hospital with an outpatient clinic for genetic counseling.

Patient Decision to Visit a Cancer Genetics Clinic

We examined the last part of the referral process, *i.e.*, the decision of a patient to visit a cancer genetics clinic among the 23 patients with whom their surgeon discussed referral to genetic counseling at a cancer genetics clinic. Of these patients, 16 of 23 (70 percent) visited a cancer genetics clinic. Within this subgroup of patients, 81 percent of the patients ($n=13$) that visited and 43 percent of patients ($n=3$) who did not visit a cancer genetics clinic were treated in a teaching hospital (Table 2). Thirty-one percent of the patients that visited ($n=5$) and 14 percent of patients ($n=1$) that did not visit a cancer genetics clinic were treated in a hospital with an outpatient clinic for genetic counseling.

Table 1. Determinants for colorectal cancer patients visiting a cancer genetics clinic

Determinant	Visited ($N=36$) N (%)	Did not visit ($N=83$) N (%)	Total ($N=119$) N (%)
Patient			
Sex, male	21 (58)	41 (49)	62 (52)
CRC below age 50 ^a	30 (83)	69 (83)	99 (83)
Second CRC below age 70	4 (11)	4 (5)	8 (7)
CRC and extracolonic cancer below age 70 ^b	2 (6)	5 (6)	7 (6)
Colorectal adenoma with high dysplasia, below age 40	0 (0)	5 (6)	5 (4)
Cancer in family ^d	20 (61)	23 (34)	43 (43)
Survival ^c	30 (83)	72 (87)	102 (86)
Professional ^d			
Documented family history	29 (88)	43 (64)	72 (72)
Documentation by surgeon of family history	17 (51)	19 (28)	36 (36)
Referral discussion	16 (48)	7 (10)	23 (23)
Hospital			
< 600 beds	6 (17)	27 (33)	33 (28)
600–800 beds	17 (47)	25 (30)	42 (35)
> 800 beds	13 (36)	31 (37)	44 (37)
Teaching hospital	33 (92)	68 (82)	101 (85)
Presence of outpatient genetics counseling clinic	15 (42)	22 (27)	37 (31)

^aCRC, colorectal cancer. ^bExtracolonic cancers: cancers associated with Lynch syndrome including carcinomas of the endometrial, ovaries, small bowel, stomach, sebaceous gland, biliary tract, and upper urinary tract. ^cSurvival was measured until the end of 2006. ^dDeterminants measured by surgical record search, 100/119 surgical records were available: 33 of patients were referred and 67 of patients were not referred to genetic counseling respectively.

Table 2. Patient decision to visit a cancer genetics clinic after referral

Determinant	Visited (N=16) N (%)	Did not visit (N=7) N (%)	Total (N=23) N (%)
Patient			
Sex, male	12 (75)	4 (57)	16 (70)
CRC below age 50 ^a	15 (94)	7 (100)	22 (96)
Second CRC below age 70	1 (6)	0 (0)	1 (4)
Cancer in family ^c	11 (69)	5 (71)	16 (70)
Survival ^b	14 (88)	5 (71)	19 (83)
Professional ^c			
Documented family history	16 (100)	5 (71)	21 (91)
Documentation by surgeon of family history	11 (69)	3 (43)	14 (61)
Hospital			
< 600 beds	4 (25)	4 (57)	8 (35)
600–800 beds	7 (44)	2 (29)	9 (39)
> 800 beds	5 (31)	1 (14)	6 (26)
Teaching Hospital	13 (81)	3 (43)	16 (70)
Presence of outpatient genetics counseling clinic	5 (31)	1 (14)	6 (26)

^aCRC, colorectal cancer. • ^bSurvival was measured until the end of 2006. • ^cDeterminants measured by surgical record search.

Determinants for the Referral Process

We analyzed for the presence of subgroups of hospitals, professionals, or patients in which the referral process was not optimally carried out. Because the determinants “family history described,” “family history described by the surgeon,” and “cancer in the family” were correlated, we chose to put “family history described” as determinant into the logistic regression model. Logistic regression analysis showed that the referral process was associated with “registration that referral was discussed” OR, 15.4; 95 percent CI, 4.1–58.3 and “teaching hospital” OR, 8.8; 95 percent CI 1.6–48.6. These characteristics accounted for 31 percent of the variance.

Because of the small number of patients (n=23) with whom the surgeon discussed referral to a cancer genetics clinic, logistic regression was unable to be performed in this subgroup. Therefore, factors that determine the referral process in this subgroup of patients could not be explored. However, univariate analysis showed an association between the referral process and hospital characteristics including size, teaching status, and presence of an outpatient clinic for genetic counseling.

DISCUSSION

Only one-third of the patients with recently diagnosed CRC that meet criteria for referral to genetic counseling visited a cancer genetics clinic. Seventy percent of patients with whom the surgeon discusses referral to a cancer genetics clinic decided to visit such a clinic. Patients with whom the surgeon discussed referral to genetic counseling and that are treated in a teaching hospital are more likely to visit a cancer genetics clinic. Determinants could not be identified for visiting a cancer genetics clinic in the subgroup of patients whom receive discussion of referral by their surgeon. These data show that the referral process to genetic counseling at a cancer genetics clinic is not optimally carried out and needs to be improved.

Identifying patients with hereditary CRC is crucial because surveillance substantially reduces morbidity and mortality.⁸ Optimal care for patients suspected of hereditary CRC includes referral to genetic counseling at a cancer genetics clinic by the treating physician. Our percentage of patients that visited a cancer genetics clinic is comparable to results of a previous study where 26 percent of clinicians recommended genetic counseling for patients with a family history consistent with Lynch syndrome.¹⁰ Another study shows that 16 percent of patients are referred to genetic counseling.¹¹ Their selection criteria are similar to ours, but slightly more patients with multiple tumors were included than patients with CRC below the age of 50 years. In contrast, in our study almost all patients had CRC below the age of 50 years.

Additionally, our study examined the existence of subgroups of hospitals, professionals, or patients in which the referral process is not optimally carried out. Patients with whom the surgeon discusses referral to genetic counseling and that are treated in a teaching hospital are more likely to visit a cancer genetics clinic. Therefore, to optimize the referral process, efforts should be concentrated on increasing referral discussions for genetic counseling by treating physicians and in increasing awareness in nonteaching hospitals. A reason not to discuss referral to a cancer genetics clinic may be the presumption that patients cannot deal with this message at a time that they receive the diagnosis of cancer. However, most patients find it highly acceptable to have the information about Lynch syndrome at the time of diagnosis.¹⁴

In our study, seventy percent of patients with whom the treating physician discussed referral to genetic counseling visited a cancer genetics clinic. Twenty-six percent of patients invited by letter for an information session about Lynch syndrome visited a cancer genetics clinic.¹² Our study and previous work suggest referral by the treating physician might be more effective than an invitation letter.

Thirty percent of patients with whom the treating physician discussed referral did not visit a cancer genetics clinic. Because of the small number of patients with whom referral to a cancer genetics clinic was discussed, we were not able to identify subgroups of patients that are more likely to visit a cancer genetics clinic after discussion of referral by their surgeon. However, in this subgroup of patients, univariate analysis showed that patients are more likely to visit a cancer genetics clinic when an outpatient clinic for genetic counseling is present in their hospital. These findings reflect the impact of both easy access to genetic counseling and higher awareness of treating physicians on the genetic counseling referral process. Univariate analysis of a study that examined determinants for access to reference care centers for patients with CRC shows that distance plays a role in the access to care.¹⁵ This trends needs to be confirmed by multivariate analysis among a larger number of patients.

Our study is unique, since it examined determinants for referral to and acceptance of genetic counseling for hereditary CRC. A limitation is some of the determinants were measured by surgical record search. For example, of the patients that visited a cancer genetics clinic, 48 percent had a notation in the surgical record that referral to genetic counseling had been discussed. This method of data collection does not monitor everything that is discussed between patient and treating physician and potentially leads to underestimation. However, to identify subgroups of patients that are more likely to visit a cancer genetics clinic, the difference between patients that visited and patients that did not visit such a clinic was used. Underestimation likely affects both groups equally. Moreover, the discussion of referral to genetic counseling at a cancer genetics clinic would likely to be registered in the surgical record. Another possibility is that the oncologist or the family doctor discussed referral to a cancer genetics clinic. Again, we expect that this rate does not differ between the two groups. Therefore, we assume that our results reflect actual clinical practice.

A 30 percent rate of uptake for genetic counseling shows that there is room for improvement in the referral process among patients who are considered to benefit from genetic counseling. The identification of patients suspected of hereditary CRC is the first and most important part of the referral process. On the one hand, the Bethesda guidelines, which describe which patients merit microsatellite instability analysis, could be implemented among clinicians involved in the care of CRC patients. On the other hand, an alternative method to identify hereditary CRC among patients with recently diagnosed CRC could be implemented. In this new method clinical practice roles have to be changed.¹⁶ The pathologist instead of the treating physician is responsible for the identification of patients suspected of hereditary CRC. The pathologist selects patients for microsatellite instability analysis of a patient's

tumor. Next, the treating physician discusses the result of microsatellite instability analysis and referral to genetic counseling with patients with a microsatellite instable tumor. With this new method, at least twice as many patients with Lynch syndrome were identified compared with current practice.¹⁶ In addition, fewer patients have to be referred to genetic counseling because patients with a microsatellite stable tumor without a family history of CRC are not considered at risk for Lynch syndrome.

CONCLUSION

Most patients with CRC at young age or with multiple cancers associated with Lynch syndrome do not visit a cancer genetics clinic according to current guidelines. To improve the referral process, improvement efforts should focus on discussion of referral by surgeons and awareness in nonteaching hospitals. In addition implementation of guidelines or a new method to detect hereditary CRC in routine clinical practice is certainly needed.

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